

REMARKS/ARGUMENTS

Claims 1, 3-12, and 26-28 are pending. Claim 2 has been cancelled. Withdrawn claims 13-25 have also been cancelled. Claims 1, 6, 7, and 8 has been amended and claims 26-28 are new. Support for the amendments to claim 1 may be found in original claim 1, the title ("concentrated [^{11}C]carbon monoxide"), and paragraph [0034] (minimization of isotopic dilution) of the published application (*i.e.*, US2007/0110664). Support for the amendments to claim 8 may be found in original claim 8. Finally, support for new claims 26-28 may be found in original claim 1 and paragraphs [0011] (carrier phosgene as a source of isotopic dilution), [0032] (nearly quantitative decay corrected radiochemical yields), and [0034] (optimization of specific radioactivity and minimization of isotopic dilution). No new matter has been introduced by way of the amendment to claims 1, 6-8, and the introduction of claims 26-28.

I. Interview Summary

The undersigned wishes to thank Examiner Perreira for the cordial and productive interview of June 17, 2011 with the undersigned and technical expert Dr. Oleksiy Itsenko (GE Healthcare). The Examiner's helpful comments and suggestions were instrumental in preparing this response. During the interview, Applicants' representative discussed the rejections under 35 U.S.C. § 103(a) and claim amendments that may overcome the art rejection. Specifically, the undersigned discussed the fact that Diksic *et al.* (*Int. J. Nucl. Med. Biol.* 9: 283-285 (1982)) does not suggest or otherwise contemplate the claimed method for producing labeled phosgene. The claimed method, unlike Diksic's, produces labeled phosgene (*e.g.*, ^{11}C -labeled phosgene), having high specific radioactivity, in high radiochemical yields. The undersigned and Dr. Itsenko pointed out that Diksic discloses a method for producing labeled phosgene that leads to the production of low specific activity phosgene. The reason why Diksic produces such low specific activity labeled phosgene is because Diksic's open, continuous flow system introduces the problem of isotopic dilution

from, e.g., cold phosgene present in the chlorine gas he uses. The Examiner agreed to reconsider the 103(a) rejections in light of evidence showing that the high specific radioactivity of the labeled phosgene made by the claimed method is a result of the minimization of isotopic dilution.

II. *Withdrawn Rejections*

Applicants wish to thank Examiner Perreira for the withdrawal of the rejection of claims 1-12 under 35 U.S.C. § 103(a) over Kihlberg *et al.* (U.S. Patent 7,521,544B2) in view of Diksic.

III. *The Modified Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn*

Claims 1-7 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Diksic in view of Suzuki *et al.* (EP0282703B1) and Shiba *et al.* (US 4,458,302) and further in view of Gascard *et al.* (*J. Phys. E: Sci. Instrum.* 15: 627-628 (1982) and further in view of Kihlberg *et al.* (US2004/0197257A1).

Claim 1, as amended, is directed to a method for labeling synthesis of phosgene. Phosgene, as the Patent Office will appreciate, has the following formula:



The method comprises providing a UV reactor assembly comprising a high pressure reaction chamber and a UV light source. The reaction chamber, in turn, comprises, a window facing a concave mirror; a first gas inlet; and a second gas inlet. The method also comprises introducing a concentrated carbon-isotope monoxide enriched gas-mixture into the reaction chamber of the UV reactor assembly via the first gas inlet. The method also comprises introducing Cl₂ gas into the reaction chamber via the second gas inlet to obtain a Cl₂-carbon-isotope monoxide gas mixture. The Cl₂-carbon-isotope monoxide gas mixture is then irradiated with UV light from the UV light source for an amount of time sufficient to

promote the labeling synthesis. The labeled phosgene is subsequently removed from the reaction chamber. The method minimizes the amount of isotopic dilution and, as a result, produces labeled phosgene with surprisingly high specific radioactivity and in high radiochemical yield.

Applicants submit that one of skill in the art could not have even expected to achieve high specific radioactivity using a continuous-flow system such as Diksic's. In his Declaration under 37 C.F.R. § 1.132, Dr. Bengt Långström explains that the reason why the skilled artisan would not have expected to achieve such high specific radioactivity is because Diksic's system introduces significant isotopic dilution from, among other things, "cold" phosgene present in the Cl₂ gas he uses. Långström Declaration at ¶ 10. In Dr. Långström's opinion as an expert having over 40 years experience in the field of ¹¹C-containing compounds, the high radioactivity and radiochemical yield achieved using the claimed method are a direct result of a significant reduction in isotopic dilution during the labelling synthesis, to the point that it becomes negligible. Such a significant reduction in isotopic dilution is, in turn, attributed to the use of small reaction volumes/amounts of reactants. Långström Declaration at ¶ 12.

According to Dr. Långström, the claimed method of making carbon-isotope labeled phosgene, including [¹¹C]phosgene, significantly differs from Diksic's method in a number of ways. First, the claimed method for synthesizing labeled phosgene involves a closed, batch system for the synthesis of the compound. The fact that the claimed method requires a "reaction chamber" implies that the system used to synthesize the labeled phosgene is a closed reaction system. Långström Declaration at ¶ 9. In contrast, Diksic's system for synthesizing labeled phosgene is an open, continuous flow system. Second, the volumes of carbon-isotope monoxide enriched gas-mixture and Cl₂ gas used in the claimed method are minute (*e.g.*, in the order of microliters) relative to the amounts of gas(es) Diksic uses. *Id.* For example, in his experiments, Diksic flows Cl₂ gas through his system at a rate of 10 mL/min and [¹¹C]carbon monoxide in carrier gas (*i.e.*, nitrogen gas) at a rate of 20-60 mL/min. Diksic at 283, right-hand column. A typical synthesis run for Diksic appears to be

ten minutes. Diksic at 284, left-hand column. Accordingly, in one synthesis run, Diksic could use 100 mL of Cl_2 gas and 200-600 mL of $[^{11}\text{C}]$ carbon monoxide in carrier gas. *Id.*

Dr. Langstrom explains in his Declaration that since Diksic uses such large volumes of gases, it is no wonder that he obtains $[^{11}\text{C}]$ phosgene with a low specific activity that is 100,000 times lower than the theoretical specific activity. Långström Declaration at ¶ 10. The use of such large volumes of gases leads to significant isotopic dilution by, *e.g.*, “cold” phosgene present in the Cl_2 gas. *Id.* Diksic suspects as much as evidenced by his statement on page 284, right-hand column: “[w]e suspect chlorine, even though we have used research purity chlorine (99.5%), since the specific activity of $[^{11}\text{C}]$ phosgene is at least 2.5×10^3 times lower than the specific activity of $[^{11}\text{C}]$ carbon monoxide.”

The ultimate consequence of the differences between the claimed method and Diksic’s is that the claimed method produces $[^{11}\text{C}]$ phosgene with significantly higher specific activity that is at least one order of magnitude higher than the specific activity of Diksic’s $[^{11}\text{C}]$ phosgene. For example, the claimed method has been shown to produce $[^{11}\text{C}]$ phosgene with a surprisingly high radioactivity of 200 GBq/ μmol , which amounts to 200 TBq/mmol, and a decay-corrected radiochemical yield of 70–85%. Långström Declaration at ¶ 11. These data and findings were presented by Oleksiy Itsenko and Tor Kihlberg (a named inventor in the captioned application), on September 10, 2010 at the 2010 World Molecular Imaging Congress in Kyoto, Japan. Moreover, these results are in agreement with the high specific radioactivity of compounds obtained using the ^{11}C -carbon monoxide produced in a similar reactor system, albeit in the context of making different compounds. *Id.*

The Patent Office attempts to cure the deficiencies in Diksic by relying on Kihlberg. Kihlberg admittedly discloses the use of, *e.g.*, $[^{11}\text{C}]$ carbon monoxide, to make various carbonyl compounds, such as aldehydes, ketones, amides, and imides using palladium-mediated chemistry; and ureas, carbamates, and carbonates using selenium-mediated chemistry. Kihlberg, however, is silent with regard to the synthesis of phosgene. Phosgene, as the Patent Office will appreciate, is structurally different (see structure above) when compared to the aforementioned carbonyl compounds. Applicants respectfully offer that the

Patent Office has done nothing more than identify a reference (Kihlberg) that teaches a starting material (^{11}CO) common to the claimed method and used to make compounds having a common function group (a carbonyl). That is where the similarities between Kihlberg and the instant claims end. For one, the structure of phosgene and that of the aforementioned carbonyl compounds is different. Also, the synthesis of such carbonyl compounds would involve the use of liquid reagents and Pd or Se catalysts, in addition to gaseous ^{11}CO . In the instant method, both reagents are gaseous. Applicants respectfully submit that the only reason to modify Kihlberg's system to synthesize phosgene is based solely on impermissible hindsight.

In addition, contrary to the Patent Office's position, it would not have been obvious to adapt Diksic's continuous flow system for synthesizing [^{11}C]-phosgene, which uses large volumes of gaseous reagents, to work in conjunction with Kihlberg's carbon-isotope monoxide-generating system, which is a closed system for making carbon-isotope monoxide. The only reason to make such a modification is based on impermissible hindsight. Further, there is nothing in Diksic suggesting that using smaller volumes of Cl_2 gas, as contemplated in the claimed method, would solve the isotopic dilution problem he identified. After all, Diksic believed that it was the grade of Cl_2 gas, and not the larger volumes used, as the source of the isotopic dilution problem.

Suzuki, Shiba, and/or Gascard do not remedy the deficiencies in Diksic. Accordingly, the claimed methods, including new method claims 26-28, are patentable over the combined teachings of Diksic, Kihlberg, Suzuki, Shiba and Gascard. Reconsideration and withdrawal of the rejection of claims 1-7 over the aforementioned references are therefore respectfully requested.

IV. *Response to Patent Office Comments*

A. Items 22 and 24

Applicants respectfully submit that Oleksiy Itsenko is not an inventor in connection with the instant application. In the response filed March 11, 2011, Dr. Itsenko was

erroneously referenced as a “named inventor.” In sum, contrary to the Patent Office’s statement in Item 24, the inventorship in connection with the captioned application is not unclear.

B. Item 25

The specification admittedly does not recite “produces [^{11}C]phosgene with a decay-corrected radiochemical yield of 70-85% and a surprisingly high radioactivity of 200GBq/micromol, which amounts to 200TBq/mmol.” As stated in the response filed March 11, 2011, however, and effectively restated by Dr. Långström in the attached declaration, the high specific activity of the [^{11}C]phosgene generated by the claimed method is a necessary result of how the method is conducted. In other words, the claimed method always generates [^{11}C]phosgene with high specific activity [^{11}C]phosgene (*e.g.*, 200GBq/ μmol) and high decay-corrected radiochemical yield (*e.g.*, 70-85%). Accordingly, the claim need not expressly state specific values for specific activity and/or decay-corrected radiochemical yield.

C. Item 26

Though Diksic arguably teaches a radiochemical of about 90%, he discloses a specific activity that is about **135 times less** than the specific activity of the [^{11}C]phosgene produced via the claimed method. What is surprising and unexpected is that the claimed method produces [^{11}C]phosgene having high specific activity **and** high decay-corrected radiochemical yield.

D. Item 28

As stated previously, Kihlberg admittedly discloses the use of, *e.g.*, [^{11}C]carbon monoxide to make various carbonyl compounds. But, Kihlberg is silent with regard to the synthesis of phosgene. The only reason to modify Kihlberg’s system to synthesize phosgene is based on impermissible hindsight. Further, it would not have been obvious to adapt Diksic’s continuous flow system for synthesizing [^{11}C]phosgene, which uses large volumes of gaseous reagents, to work in conjunction with Kihlberg’s carbon-isotope monoxide-

generating system, which is a closed system for making carbon-isotope monoxide. In sum, the combined teachings of Diksic and Kihlberg do not render the claimed method obvious.

V. *The Obviousness-Type Double Patenting Rejection Should Be Held in Abeyance*

Claims 1-7 stand rejected under the judicially-created doctrine of obviousness-type double patenting (ODP) as being unpatentable over claims 1-7 of U.S. Patent No. 7,521,544 in view of Diksic. Claims 8-12 stand provisionally rejected under ODP as being unpatentable over claims 8-11 of co-pending Appl. Ser. No. 12/423,034.

While not acquiescing to the propriety of any of the ODP rejections enumerated above, Applicants respectfully submit that once the claims of the instant application are held to be otherwise allowable, Applicants will consider filing a duly executed terminal disclaimer to overcome the ODP rejections. In the meantime, Applicants respectfully request that all of the ODP rejections be held in abeyance.

VI. *The Rejections Under 35 U.S.C. § 102(b) Should be Withdrawn*

Claims 8, 9, and 11 stand rejected under 35 U.S.C. § 102(b) as being unpatentable over Shi *et al.* (U.S. Patent No. 6,284,050). Applicants respectfully submit that Shi does not expressly or inherently disclose all of the features claimed in claims 8, 9, and 11. For example, Shi does not disclose a system comprising, among other things, a concentrated carbon-isotope monoxide gas source; a Cl₂ gas source; a first gas inlet for admitting concentrated carbon-isotope monoxide enriched gas-mixture into the reaction chamber from the concentrated carbon-isotope monoxide gas source; and a second gas inlet for admitting Cl₂ gas from the Cl₂ gas source. Accordingly, Shi does not anticipate claims 8, 9, and 11. Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Applicants respectfully note that claim 10 has not been rejected over Shi. Applicants therefore request an indication from the Patent Office that claim 10 is patentable over Shi.

VII. *The New Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn*

Claims 8, 9, 11, and 12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Suzuki in view of Shi, Shiba and further in view of Maag *et al.* (U.S. Patent No. 6,472,026) and Gadgil *et al.* (U.S. Patent No. 5,780,860). Applicants respectfully note that claim 10 has not been rejected over these references. Applicants therefore request an indication from the Patent Office that claim 10 is patentable over these references.

As an initial matter, the references cited are not analogous art. A reference qualifies as prior art for an obviousness determination under § 103 only when it is analogous to the claimed invention. *In re Klein*, U.S.P.Q.2d 1991, 1993 (Fed. Cir. 2011 (citations omitted)). Two separate tests define the scope of analogous prior art: (1) whether the art is from the same field of endeavor, regardless of the problem addressed and, (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved." *Id.* A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem. *Id.*

The field of endeavor with regard to the instant system claims is the batch-wise photochemical synthesis of carbon-isotope labeled phosgene using chlorine gas and carbon-isotope monoxide. The field of endeavor of Shi is UV light-assisted chemical vapor deposition on a semiconductor wafer. The field of endeavor of Shiba is a reflection-type optical focusing apparatus for semiconductor fabrication. Similarly, the field of endeavor of Suzuki is treating semiconductor wafers with UV-light. The field of endeavor of Maag is UV-curing of lacquer coatings for the automobile industry. Finally, the field of endeavor for

Gadgil is a UV disinfecter of water and other liquid streams. Applicants respectfully submit that none of these field of endeavors are even remotely within the same field of endeavor as the inventions claimed in claims 8, 9, 11, and 12.

Further, the references are not reasonably pertinent to the particular problem with which the inventors are involved. The problem sought to be solved by the claimed system is isotopic dilution in the synthesis of carbon-isotope labeled phosgene. The way that the problem is solved is by synthesizing the labeled phosgene in a closed, batch system, such as the one claimed. None of the cited references are seeking to solve this problem or even a remotely similar problem (*e.g.*, the synthesis of chemical compounds). Accordingly, the cited references are not analogous art and, as a result, do not qualify as prior art for an obviousness determination under § 103. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Even if the Patent Office were to hold the cited references as analogous art, the references, even if combined, do not suggest or otherwise contemplate all of the claimed features in claims 8, 9, 11, and 12. Claim 8, from which claims 9, 11, and 12 depend, requires a system comprising the recited gas inlets and gas sources. The skilled artisan would be hard-pressed to use a chlorine gas source, as presently claimed, in the context of semiconductor fabrication (Shi, Shiba, and Suzuki), lacquer coating fabrication for the automobile industry (Maag) or in water/liquid "disinfection" (Gadgil). That is because chlorine gas is extremely corrosive and would not be compatible with any of those fields of endeavor. In sum, even if held to be analogous art, the cited references, alone or in combination, would not render the claimed system obvious. For at least this additional reason, Applicants respectfully request reconsideration and withdrawal of this rejection.

Applicants conclude, on the basis of the above argumentation, that the pending claims are patentable and request favorable consideration.

Appl. No. 10/581,835
Reply to Office Action of March 31, 2011

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,

/Robert F. Chisholm/
Robert F. Chisholm
Registration No.: 39,939

GE Healthcare, Inc.
101 Carnegie Center
Princeton, New Jersey 08540-6231
Tel: (609) 514-6905
Fax: (609) 514-6572